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Review Paper

2,3,7,8-Tetrachlorodibezo-p-dioxin exposure and prostate cancer: a meta-analysis of cohort studies

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ABSTRACT

Objective: To perform a meta-analysis of cohort studies and evaluate the association between exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and prostate cancer quantitatively.

Study design: Publications before April 2012 about populations exposed to TCDD were searched in PubMed. Only cohort studies were included. Extraction and quality assessment of included articles was performed independently by two authors using the MOOSE guidelines.

Methods: A total of 17 cohort studies on prostate cancer with information about standardized mortality ratios (SMR), risk ratio (RR), standardized incidence ratios (SIR) and TCDD exposure were included. SMRs and RRs were pooled separately after weighing each study by calculating the inverse of the estimated variance.

Results: Based on the 13 reported SMRs or SIRs, the meta-analysis yielded a meta-SMR of 1.26 (95% confidence interval 1.00–1.57, $P = 0.046$). The meta-RR, based on four reported RR from four cohorts, was 1.04 (95% confidence interval 0.85–1.28). Begg's funnel plot showed little evidence of publication bias (Egger's test P-value = 0.817).

Conclusion: This meta-analysis suggests that exposure to TCDD is associated with increased risk of prostate cancer.

Introduction

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is a widespread environmental contaminant,[1] and it is the most toxic halogenated aromatic hydrocarbon.[2] TCDD is a multisite carcinogen.[3] Long-term TCDD exposure leads to the development of tumours of the liver, thyroid, lung, skin, oral cavity, ovary and other sites in animal experiments.[3,4] The last full-scale International Agency for Research on Cancer (IARC) Monographs review, completed in 1997, classified TCDD as a human carcinogen.[5] However, this claim has been challenged recently.[6,7] Therefore, it is still

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controversial whether TCDD could exhibit carcinogenic effect in humans.

The incidence of prostate cancer has increased over recent decades and it is now the most commonly diagnosed cancer among men in Europe and USA.[8,9] While the prostate cancer incidence remains lower in Asian countries than in North America, there is still a remarkable increase in the mortality in China, Japan, Korea and Singapore.[10,11] The current knowledge of the aetiology of prostate cancer is limited and the cause of prostate cancer remains speculative. Both in-vivo and in-vitro experiments suggest that TCDD, acting as an endocrine disruptor, may contribute to the development of certain cancers, including prostate cancer.[12,13] Because the epidemiological investigations are not conclusive, a meta-analysis was performed to evaluate the association between exposure to TCDD and prostate cancer quantitatively.

Methods

Data sources

Publications before April 2012 about populations exposed to TCDD were searched in PubMed. The search was conducted using several combinations of the following key words in the full text: prostatic neoplasm, prostate cancer, cancer of the prostate, prostate carcinoma, neoplasm, cancer, carcinoma, TCDD, cohort, standardized mortality ratio (SMR), risk ratio (RR), and standardized incidence ratio (SIR). References cited in the selected articles were also considered.

Study selection

The studies included in the meta-analysis should meet the following criteria:

(1) Cohort studies were published in English in peer reviewed journals. The publication date was before April, 2012;
(2) The cohort was a population with unequivocal evidence of exposure to TCDD (for example herbicide workers exposed to 2,4,5-trichlorophenol (TCP) and 2,4,5-Trichlorophenoxyacetic acid (2,4,5-T) and Veterans of the Vietnam War exposed to Agent Orange);[14]
(3) The cause-specific deaths were classified by the International Classification of Diseases (ICD) code;
(4) The SMR, SIR or RR was reported;
(5) The report provided sufficient data to determine the estimate and confidence intervals of SMR or RR.

Studies were excluded from the analysis if they:

(1) included subjects that were already included in another more complete or more recent study of a similar design, or these subjects were already included in a study with a longer follow-up time;
(2) did not report original results (reviews, comments, letters, and editorials);
(3) were population- or hospital-based case–control studies, or nested case–control studies that were with only limited documentation of TCDD exposure.

Data extraction

The articles and the extracted data were reviewed independently by two investigators (Ling Leng and Xiao-yan Luo), and any disagreement was resolved by consulting with a third reviewer (Chang-ping Li). The following information was recorded for each study: first author, year of publication, country, major chemicals exposed to, exposure setting, cohort size, observed deaths, average person-year, SMR/SIR/RR and 95% confidence interval (CI) for prostate cancer.

Statistical analysis

In recent publications, RR was calculated by comparing the mortality of two groups, while SMR was used more often in the past. Due to the differences between these two statistics, SMRs and RRs were pooled separately.[15] There was only one SIR included in this analysis, so it was pooled with SMR. Log-transformed 95% CIs were calculated for estimating the standard errors (SEs) for the ln(SMR) or ln(RR) by the formula: $SE = [\ln(\text{upper limit}) - \ln(\text{lower limit})] \div (2 \times Z_{1-\alpha/2})$, where for a 95% CI, $Z_{1-\alpha/2}$ equals 1.96.[16] For studies in which there was zero observed and expected events, 1 was added to both the observed and expected number of events so that an estimate of ln(SMR)/ln(SIR) and its associated standard error could be calculated.[17]

Overall pooled SMR estimates and their corresponding 95% CIs were obtained using fixed-effects (Mantel–Haenszel method) or random-effects (DerSimonian and Laird method) methods, weighing each study by measuring its precision as the inverse of the estimated variance.[18] When there is no detectable heterogeneity, the two estimates coincide. Heterogeneity of effects across studies was assessed by the Cochrane's Q statistic and was deemed significant when $P < 0.05$. In addition, the coefficient of inconsistency (I^2) as described by Higgins and Thompson was also computed to assess the heterogeneity.[19] I^2 is an estimate of the proportion of total variation that is due to heterogeneity. $I^2 > 25\%$ indicates significant heterogeneity.[16] Sensitivity analysis was conducted to determine whether the meta-SMR or meta-RR differed due to different study characteristics. Publication bias was evaluated by visual inspection of Begg's funnel plots and confirmed using Egger's regression asymmetry method.[20]

The meta-analysis was performed with Stata software (version 11; StataCorp LD, College Station, TX, USA) using a combination of available macros. A P-value <0.05 was considered statistically significant and would be indicated with an asterisk (*).

Results

Literature search

Overall, 319 citations were identified by using several combinations of key words, with 207 duplicate records. After removing duplicate citations, 112 citations were screened on basis of the title and abstract. 69 records were excluded for the following reasons: a, articles that were not population studies; b, articles did not report original results (reviews, comments,